DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse in the reply filed 3/20/2008 is acknowledged. Applicant's argument that restriction between Groups I-IV is improper is persuasive. The election/restriction requirements mailed 9/27/2007 and 12/31/2007 are vacated. A new election/restriction requirement appears below.

2. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows: isopropanol, urea, arginine, aspartic acid, calcium chloride, methanol, ethanol, tert-butanol, acetonitrile, dimethylformamide, ethylene glycol, propylene glycol, acetic acid and dioxin.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

3. The claims are deemed to correspond to the species listed above in the following manner: isopropanol, claims 19-24, 88-97 and 132; urea, claims 2 and 84-87; arginine, claims 4-8; aspartic acid, claims 9-13; calcium chloride, claims 14-18; methanol, claims 25-30; ethanol, claims 31-36; tert-butanol, claims 38-42; acetonitrile, claims 43-48; dimethylformamide, claims 49-54; ethylene glycol, claims 61-66; propylene glycol, claims 67-72; acetic acid, claims 73-78 and dioxin, claims 79-83.

The following claim(s) are generic: 1, 3, 98, 99-105, 130, 131 and 133-142.

4. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the compounds have different chemical structures and therefore lack unity of invention *a priori*.

5. During a telephone conversation with O.M. Zaghmout on 6/2/2008 a provisional election was made with traverse to prosecute the species isopropanol. Affirmation of this election must be made by applicant in replying to this Office action. A prior art rejection is made over the elected species as well as over the additional species ethanol, methanol, and dioxin. As a result the search has not been extended to additional species. Claims 2, 4-18, 37-78, 84-87, 98 and 136 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
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> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Annibali (US Patent No. 7.091,032). Annibali teaches a process for the recovery of recombinant insulin comprising treating the culture medium with a water miscible solvent, methanol, to induce expression, wherein the pH of the culture medium is maintained between 3.5 to 5.5 (col. 25, lines 1-35).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 25, 99-101, 130, 131, 135, 137-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Annibali (US Patent No. 7,091,032) in view of Willis (*Modern Drug Discov.*, **2001**, *4*, 43-44). Annibali teaches a process for the expression of recombinant insulin in *P. Pastoris* comprising treating the culture medium with a water miscible solvent, methanol, to induce expression, wherein the pH of the culture medium is maintained between 3.5 to 5.5, followed by purification with cation exchange chromatography (col. 25, lines 1-35). Annibali does not teach the use of expanded-bed chromatography. Willis teaches that expanded-bed chromatography is a technique that combines the step of sample preparation with the first stage of chromatography, and is advantageous for use in methods for purification of recombinantly expressed proteins in cells. It would have been obvious to the skilled artisan to substitute expanded-bed chromatography taught by Willis for the traditional chromatography in the method taught by Annibali, satisfying all of the limitations of claims 1, 25, 99-101, 130, 131, 137-142. With respect to claim 135, Annibali also teaches that the methanol is added with glycerol and trace salts (col. 25, lines 21 and 25). The skilled artisan would have been motivated to make the substitution based on the teaching of Willis: "The advantage is a higher recovery," says Guenter Jagschies, vice president of industrial separations for Amersham Biosciences. "That's where the money comes out for the customer." Jagschies says that EBA users often see a 25% increase in their recovery. "That is very important," he continues, "because we are talking about the first step in the downstream process, and you can never have more product after any later step. You always lose something." There would have been a reasonable expectation of success given that expanded-bed chromatography supplies are commercially available (Willis). Thus, the invention

as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 25, 99-105, 130, 131, 135, 137-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Annibali (US Patent No. 7.091,032) and Willis (*Modern Drug Discov.*, **2001**, *4*, 43-44), as applied to claims 1, 25, 99-101, 130, 131, 135, 137-142 above, in further view of Trinh *et al.* (*Bioseparation*, **2000**, *9*, 223-30) and Scopes (Protein Purification: Principles and Practice, Springer, New York, 1994, pp 157-71). Neither Annibali or Willis teach the use of Streamline-SP cation exchange resin or the particular claimed buffers. Trinh *et al.* teach a method for purifying a recombinant protein from *P. Pastoris* using Streamline-SP cation exchange resin as an expanded-bed chromatography step. Scopes teaches general methods for ion exchange chromatography including the selection of buffers and loading, washing and eluting conditions. It would have been obvious to the skilled artisan to use the Streamline-SP cation exchange resin taught by Trinh *et al.* because it is a commercially available expanded-bed resin that can be used to purify recombinant proteins from *P.Pastoris*. It would have been further obvious to select buffers and load, wash and elution conditions based on the isoelectric point of insulin according to the known and routine practices of the protein purification art as taught by Scopes. It is routine in the protein purification art to vary chromatography conditions in order to improve purification protocols and yields. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 1, 3, 19-36, 79-83, 88-97, 99-101, 130-135, and 137-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Annibali (US Patent No. 7.091,032) in view of Willis (*Modern Drug Discov.*, **2001**, *4*, 43-44), as applied to claims 1, 25, 99-101, 130, 131, 135, 137-

142 above in further view of Scopes (Protein Purification: Principles and Practice, Springer, New York, 1994, pp 85-93) and Gerlough & Bates (*J. Pharm. Exp. Therapeutics*, **1932**, Vol. XLV, No. 1, pp. 19-51).

Annibali teaches a process for the expression of recombinant insulin in *P. Pastoris* comprising treating the culture medium with a water miscible solvent, methanol, to induce expression, wherein the pH of the culture medium is maintained between 3.5 to 5.5, followed by purification with cation exchange chromatography (col. 25, lines 1-35). Annibali does not teach the use of expanded-bed chromatography or the addition of other water miscible organic solvents to the culture medium to purify the recombinant insulin.

Willis teaches that expanded-bed chromatography is a technique that combines the step of sample preparation with the first stage of chromatography, and is advantageous for use in methods for purification of recombinantly expressed proteins in cells.

Gerlough & Bates teach a method of purifying insulin comprising alcohol precipitation of insulin (pages 20 and 21). Specifically, minced beef pancreas were extracted in 60 to 65 per cent alcohol acidulated with HCl; the extract centrifuged off, neutralized to precipitate the bulk of the physiologically inert proteins and then filtered. The clear alcoholic filtrate was acidified to approximately pH 3.3 and concentrated to one-tenth its volume. Then $(NH_4)_2SO_4$ was added to salt out the insulin together with a large quantity of inert proteins. The precipitant was defatted with an alcohol-ether mixture, dried and the dispersed in water. The reaction was maintained between pH 2.5 and 2.8. The crude insulin was again salted out by the addition of Na_2SO_4. The wet precipitate was taken up in water and alcohol. The insoluble precipitate was centrifuged off, dispersed in water and extracted with 60 per cent alcohol. The precipitate was again centrifuged

off and reextracted a third time. All of the extracts were combined, precipitated in 90 to 92 per cent alcohol. The precipitate was washed with ether, dried and then taken up with water and reprecipitated three times isoelectrically at pH 5.0 to remove slats ad inert soluble pancreas protein.

Scopes teaches that the method of protein precipitation by water-miscible organic solvents has been employed since the early days of protein purification (page 85). The two most widely used solvents are ethanol and acetone (page 87). Others that can be used include methanol, isopropanol, and dioxin (page 87). The first step can involve the addition of 20-30% solvent, increasing in subsequent steps to 50% (pages 88-89).

It would have been obvious to the skilled artisan to substitute expanded-bed chromatography taught by Willis for the traditional chromatography in the method taught by Annibali, satisfying all of the limitations of claims 1, 25, 99-101, 130, 131, 137-142. With respect to claim 135, Annibali also teaches that the methanol is added with glycerol and trace salts (col. 25, lines 21 and 25). With respect to claims 3, 19-24, 26-36, 79-83, 88-97 and 132-135, it would have been further obvious to add a precipitation step to the purification protocol, according to the teaching of Gerlough & Bates and Scopes. All of the elements of the claimed methods were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods and through routine experimentation, with no change in their respective functions, to yield the predictable result of insulin purification. It is routine in the protein purification art to combine different methods of separation, precipitation, chromatography and dialysis to improve purification protocols. Thus, the invention as a whole

was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday, 9:00 A.M. to 3:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654